

WHAT IS CLAIMED IS:

1. A method to treat a reduction in blood flow to the central nervous system, the method comprising:

(a) diagnosing a subject in need of treatment for a reduction in blood flow to the central nervous system; and

5 (b) administering to the subject a cyclooxygenase-2 selective inhibitor or an isomer, a pharmaceutically acceptable salt, ester, or prodrug of a cyclooxygenase-2 selective inhibitor and an amphetamine or an isomer, a pharmaceutically acceptable salt, ester, or prodrug of an amphetamine.

2. The method of claim 1 wherein the cyclooxygenase-2 selective inhibitor has a selectivity ratio of COX-1 IC_{50} to COX-2 IC_{50} not less than about 50.

3. The method of claim 1 wherein the cyclooxygenase-2 selective inhibitor has a selectivity ratio of COX-1 IC_{50} to COX-2 IC_{50} not less than about 100.

4. The method of claim 1 wherein the cyclooxygenase-2 selective inhibitor is selected from the group consisting of celecoxib, deracoxib, valdecoxib, rofecoxib, etoricoxib, meloxicam, parecoxib, 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide, 2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one, N-[2-
5 (cyclohexyloxy)-4-nitrophenyl]methanesulfonamide, 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone, 2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid, (3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone, and (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid.

5. The method of claim 1 wherein the amphetamine is selected from the group consisting of phenylethylamine, dextroamphetamine, methamphetamine, amphetamine aspartate, amphetamine sulfate, dextroamphetamine saccharate, dextroamphetamine sulfate methylphenidate, and methylamphetamine.

6. The method of claim 4 wherein the amphetamine is selected from the group consisting of phenylethylamine, dextroamphetamine, methamphetamine, amphetamine aspartate, amphetamine sulfate, dextroamphetamine saccharate, dextroamphetamine sulfate methylphenidate, and methylamphetamine.

7. The method of claim 1 wherein the reduction in blood flow to the central nervous system results from a vaso-occlusive event selected from the group consisting of myocardial infarction, stroke, amaurosis fugax, aortic stenosis, cardiac stenosis, carotid artery stenosis, coronary stenosis and pulmonary stenosis.

8. A method to treat a reduction in blood flow to the central nervous system, the method comprising:

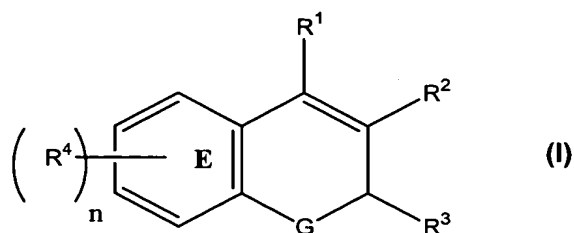
(a) diagnosing a subject in need of treatment for a reduction in blood flow to the central nervous system; and

5 (b) administering to the subject a cyclooxygenase-2 selective inhibitor that is a chromene compound, the chromene compound comprising a benzothiopyran, a dihydroquinoline or a dihydronaphthalene or an isomer, a pharmaceutically acceptable salt, ester, or prodrug of the chromene compound and an amphetamine or an isomer, a pharmaceutically acceptable salt, ester, or prodrug of an amphetamine.

9. The method of claim 8 wherein the cyclooxygenase-2 selective inhibitor has a selectivity ratio of COX-1 IC_{50} to COX-2 IC_{50} not less than about 50.

10. The method of claim 8 wherein the cyclooxygenase-2 selective inhibitor has a selectivity ratio of COX-1 IC_{50} to COX-2 IC_{50} not less than about 100.

11. The method of claim 8 wherein the cyclooxygenase-2 selective inhibitor is a compound having the formula



wherein:

n is an integer which is 0, 1, 2, 3 or 4;

5 G is O, S or NR^a ;

R^a is alkyl;

R^1 is selected from the group consisting of H and aryl;

R^2 is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

- 10 R^3 is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from alkylthio, nitro and alkylsulfonyl; and
- each R^4 is independently selected from the group consisting of H, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy,
- 15 alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, hydroxyarylcarbonyl, nitroaryl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl; and
- 20 R^4 together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical.

12. The method of claim 11 wherein:

n is an integer which is 0, 1, 2, 3 or 4;

G is O, S or NR^b ;

R^1 is H;

5 R^b is alkyl;

R^2 is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxy carbonyl;

R^3 is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl, wherein haloalkyl, alkyl, aralkyl, cycloalkyl, and aryl each is independently optionally

10 substituted with one or more radicals selected from the group consisting of alkylthio, nitro and alkylsulfonyl; and

each R^4 is independently selected from the group consisting of hydrido, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino,

15 aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl; or wherein R^4 together with ring E forms a naphthyl radical.

13. The method of claim 11 wherein:

n is an integer which is 0, 1, 2, 3 or 4;

G is oxygen or sulfur;

R¹ is H;

5 R² is carboxyl, lower alkyl, lower aralkyl or lower alkoxy carbonyl;

R³ is lower haloalkyl, lower cycloalkyl or phenyl; and

each R⁴ is H, halo, lower alkyl, lower alkoxy, lower haloalkyl, lower haloalkoxy, lower alkylamino, nitro, amino, aminosulfonyl, lower alkylaminosulfonyl, 5-membered heteroarylalkylaminosulfonyl, 6-membered heteroarylalkylaminosulfonyl, lower
10 aralkylaminosulfonyl, 5-membered nitrogen-containing heterocyclosulfonyl, 6-membered-nitrogen containing heterocyclosulfonyl, lower alkylsulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, or lower alkylcarbonyl; or

wherein R⁴ together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical.

14. The method of claim 11 wherein:

R² is carboxyl;

R³ is lower haloalkyl; and

each R⁴ is H, halo, lower alkyl, lower haloalkyl, lower haloalkoxy, lower alkylamino,
5 amino, aminosulfonyl, lower alkylaminosulfonyl, 5-membered heteroarylalkylaminosulfonyl, 6-membered heteroarylalkylaminosulfonyl, lower aralkylaminosulfonyl, lower alkylsulfonyl, 6-membered nitrogen-containing heterocyclosulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, or lower alkylcarbonyl; or wherein R⁴ together with ring E forms a naphthyl radical.

15. The method of claim 8 wherein the cyclooxygenase-2 selective inhibitor is (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid.

16. The method of claim 8 wherein the amphetamine is selected from the group consisting of phenylethylamine, dextroamphetamine, methamphetamine, amphetamine aspartate, amphetamine sulfate, dextroamphetamine saccharate, dextroamphetamine sulfate methylphenidate, and methylamphetamine.

17. The method of claim 8 wherein the reduction in blood flow to the central nervous system results from a vaso-occlusive event selected from the group consisting of myocardial infarction, stroke, amaurosis fugax, aortic stenosis, cardiac stenosis, carotid artery stenosis, coronary stenosis and pulmonary stenosis.

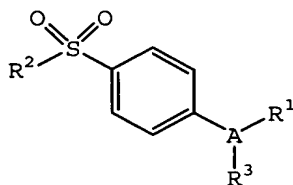
18. A method to treat a reduction in blood flow to the central nervous system, the method comprising:

- (a) diagnosing a subject in need of treatment for a reduction in blood flow to the central nervous system; and
- (b) administering to the subject a cyclooxygenase-2 selective inhibitor that is a tricyclic compound, the tricyclic compound comprising a benzenesulfonamide or methylsulfonylbenzene or an isomer, a pharmaceutically acceptable salt, ester, or prodrug of the tricyclic compound and an amphetamine or an isomer, a pharmaceutically acceptable salt, ester, or prodrug of an amphetamine.

19. The method of claim 18 wherein the cyclooxygenase-2 selective inhibitor has a selectivity ratio of COX-1 IC_{50} to COX-2 IC_{50} not less than about 50.

20. The method of claim 18 wherein the cyclooxygenase-2 selective inhibitor has a selectivity ratio of COX-1 IC_{50} to COX-2 IC_{50} not less than about 100.

21. The method of claim 18 wherein the cyclooxygenase-2 selective inhibitor is a compound of the formula:



wherein:

- 5 A is selected from the group consisting of partially unsaturated or unsaturated heterocyclyl and partially unsaturated or unsaturated carbocyclic rings;
- R^1 is selected from the group consisting of heterocyclyl, cycloalkyl, cycloalkenyl and aryl, wherein R^1 is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxy carbonyl, hydroxyl, hydroxyalkyl,
- 10 haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;
- R^2 is selected from the group consisting of methyl or amino; and
- R^3 is selected from the group consisting of a radical selected from H, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocycloxy, alkyloxy, alkylthio,

- 15 alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N- arylaminocarbonyl, N-alkyl-N-
20 arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-aryl amino, N- aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-aryl amino, aminoalkyl, alkylaminoalkyl, N-aryl aminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-aralkylaminoalkyl, N-alkyl-N- arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, N-alkyl-N-
25 arylaminosulfonyl.

22. The method of claim 18 wherein the cyclooxygenase-2 selective inhibitor is selected from the group consisting of celecoxib, valdecoxib, parecoxib, deracoxib, rofecoxib, etoricoxib, and 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.

23. The method of claim 18 wherein the amphetamine is selected from the group consisting of phenylethylamine, dextroamphetamine, methamphetamine, amphetamine aspartate, amphetamine sulfate, dextroamphetamine saccharate, dextroamphetamine sulfate methylphenidate, and methylamphetamine.

24. The method of claim 18 wherein the reduction in blood flow to the central nervous system results from a vaso-occlusive event selected from the group consisting of myocardial infarction, stroke, amaurosis fugax, aortic stenosis, cardiac stenosis, carotid artery stenosis, coronary stenosis and pulmonary stenosis.

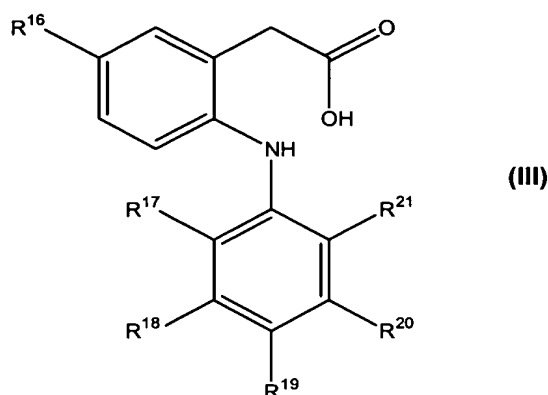
25. A method to treat a reduction in blood flow to the central nervous system, the method comprising:

- (a) diagnosing a subject in need of treatment for a reduction in blood flow to the central nervous system; and
- (b) administering to the subject a cyclooxygenase-2 selective inhibitor that is a phenyl acetic acid compound or an isomer, a pharmaceutically acceptable salt, ester, or prodrug of the phenyl acetic acid compound and an amphetamine or an isomer, a pharmaceutically acceptable salt, ester, or prodrug of an amphetamine.

26. The method of claim 25 wherein the cyclooxygenase-2 selective inhibitor has a selectivity ratio of COX-1 IC_{50} to COX-2 IC_{50} not less than about 50.

27. The method of claim 25 wherein the cyclooxygenase-2 selective inhibitor has a selectivity ratio of COX-1 IC_{50} to COX-2 IC_{50} not less than about 100.

28. The method of claim 25 wherein the cyclooxygenase-2 selective inhibitor is a compound having the formula:



wherein:

- 5 R^{16} is methyl or ethyl;
 R^{17} is chloro or fluoro;
 R^{18} is hydrogen or fluoro;
 R^{19} is hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or hydroxy;
 R^{20} is hydrogen or fluoro;
 10 R^{21} is chloro, fluoro, trifluoromethyl or methyl; and
 provided that R^{17} , R^{18} , R^{19} and R^{20} are not all fluoro when R^{16} is ethyl and R^{19} is H.

29. The method of claim 28 wherein:

- R^{16} is ethyl;
 R^{17} and R^{19} are chloro;
 R^{18} and R^{20} are hydrogen; and
 5 and R^{21} is methyl.

30. The method of claim 25 wherein the amphetamine is selected from the group consisting of phenylethylamine, dextroamphetamine, methamphetamine, amphetamine

aspartate, amphetamine sulfate, dextroamphetamine saccharate, dextroamphetamine sulfate methylphenidate, and methylamphetamine.

31. The method of claim 25 wherein the reduction in blood flow to the central nervous system results from a vaso-occlusive event selected from the group consisting of myocardial infarction, stroke, amaurosis fugax, aortic stenosis, cardiac stenosis, carotid artery stenosis, coronary stenosis and pulmonary stenosis.